Cardiomyopathy

Introduction

This lesson is about cardiomyopathies, the failure of the heart to do what it should. Cardio: heart; myo: muscle; pathy: *done broke*. But it must be outside of any other context, to the exclusion of secondary heart disease—no hypertension, no ischemia, no valvular disorder. "Cardiomyopathy" is functionally a diagnosis of exclusion which means, "the heart *done broke,* but we don't know why."

There are three **patterns** of anatomic abnormalities of the heart. They fall into three pathologic patterns: dilated cardiomyopathy (dilated ventricles but not thickened myocardium), hypertrophic cardiomyopathy (no dilation, but thickened myocardium), and restrictive cardiomyopathy (neither dilated nor thickened).

CARDIOMYOPATHY	GROSS FINDINGS	ECHOCARDIOGRAM	CAUSES	SECONDARY MIMICKERS
Dilated	All four chambers are dilated, eccentric hypertrophy	EF < 40%	Genetic Alcohol Doxorubicin Peripartum	Ischemic heart disease Valvular Congenital heart
Hypertrophic	Asymmetric septal hypertrophy (subaortic stenosis) and left ventricle concentric hypertrophy	EF 50%–70%	Genetic HOCM = Sarcomeres Friedreich ataxia	Hypertensive heart disease Aortic stenosis
Restrictive	Not dilated and not hypertrophic	EF 70%–90%	Amyloidosis Sarcoidosis Hemochromatosis Cancer and fibrosis	Constrictive pericarditis

Table 8.1: Anatomic Variations of Primary Cardiomyopathy

Although chronic myocardial dysfunction secondary to ischemia, valvular abnormalities, or hypertension can cause significant ventricular dysfunction, these conditions should not be denoted as cardiomyopathies. They are therefore **diagnoses of exclusion** named by their **anatomic presentation** and not necessarily by their pathogenesis. Reliably, however, dilated cardiomyopathy impairs systolic function, restrictive cardiomyopathy impairs diastolic function, and hypertrophic obstructive cardiomyopathy results in outflow tract obstruction.

In the literature regarding heart failure, the word *cardiomyopathy* is commonly used inappropriately. We even did it in the last lesson. Ischemic cardiomyopathy is the term used to communicate heart failure with a reduced ejection fraction secondary to coronary artery disease. There, cardiomyopathy is used not in the histologic/pathologic sense, but as a diagnosis. In this lesson we are going to use this word strictly and correctly. Cardiomyopathy is defined as a structural change to the heart chambers with a cause other than hypertension, valvular disease, or coronary ischemia.

We discuss the three major categories, compare them to secondary forms of heart changes, and throw in takotsubo and some comments on myocarditis to round out the discussion.

Dilated Cardiomyopathy

In dilated cardiomyopathy, **all four chambers dilate**. Dilation is the result of **eccentric hypertrophy**, the stacking of more sarcomeres end to end within each myocyte, making the myocytes longer. Just like heart failure with reduced ejection fraction, too much eccentric hypertrophy alters the geometric shape of the heart. Dilated cardiomyopathy (DCM) means the heart organ has gotten bigger (hypertrophy) from larger volume (eccentric) and not because the mass of myocardium has increased.

With dilation, the chambers stretch, **compromising ejection fraction**, and ultimately resulting in severe wall motion abnormalities. As the chambers dilate, fraction progressively declines. With more sarcomeres, with longer myocytes, the work done by the myocytes goes up without a compensatory increase in vasculature, predisposing the dilated heart to ischemic injury and **arrhythmia**. Since cardiomyopathies are diagnoses of exclusion, dilation of a chamber because of a valve abnormality (mitral valve regurgitation) would not be considered a dilated cardiomyopathy. However, because the ventricles dilate, there may be a secondary valve failure because of the dilated cardiomyopathy. This is frustrating, since dilation of a chamber increases risk of arrhythmia, and dilation of a ventricle reduces ejection fraction, but dilation of all chambers is required for the diagnosis of "dilated cardiomyopathy."

Look for **dilation of all four chambers**, **impaired ejection fraction**, and **no coronary artery disease**.

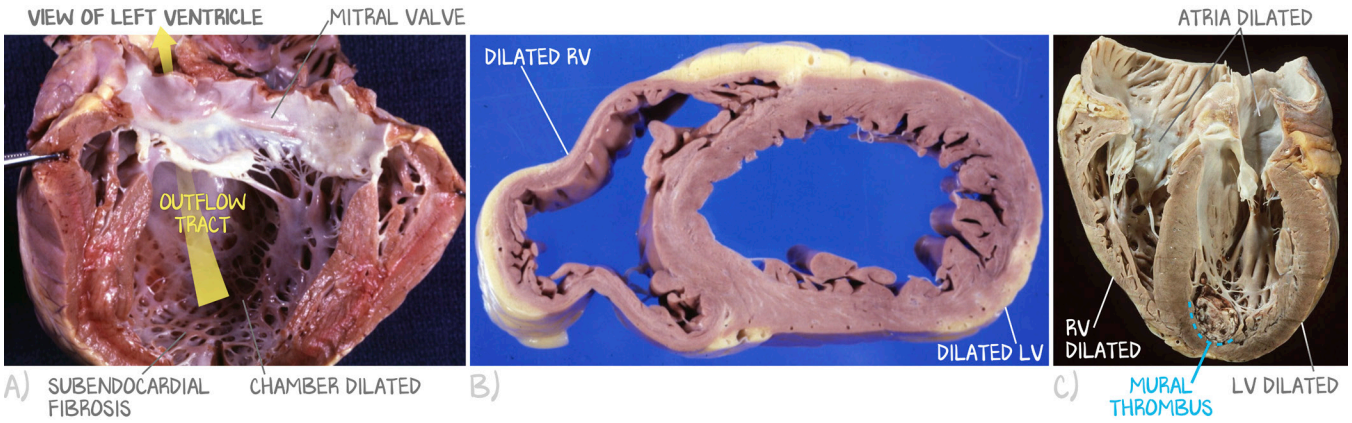

Figure 8.1: Dilated Cardiomyopathy
(a) A dilated left ventricle as seen from the anterior, with the anterior wall removed. The papillary muscles and chordae tendineae are useful for orientation, as the tendineae always go up from the papillary muscles to the mitral valve. Here, the mitral valve is stretched, obscuring the left ventricular outflow and aorta underneath. The chamber is very dilated and is lined with a white frosting. The white on the trabecular muscle is fibrosis. Because it is on the endocardium only (on the muscle as seen in the chamber) and not in the myocardium (as seen by the absence of white in the ventricular wall), this is termed subendocardial fibrosis. (b) A cross-section through both the left and right ventricle reveals both chambers as dilated (we assume you've seen enough normal so far that an orientation figure was unnecessary). (c) The front of both ventricles has been removed, as have the top and front of the atria. This was a means of showing all four chambers as being dilated as well as a mural thrombus in the apex of the left ventricle. This heart was fixed in a way that did not preserve its natural color, so the subendocardial fibrosis (which is present) is harder to see than in (a). In this four-chamber view, all chambers appear dilated.

It is the most common anatomic pattern. It is often idiopathic. Some causes with notes are included.

Autosomal dominant titin mutation	Titin is the mechanism by which stretch is resisted, which keeps the ventricle from overstretching, applying passive tension. Its absence or deficiency leaves the myocardium vulnerable to stretch.
Alcohol use	Alcohol can be toxic to the myocardium.
B_1 deficiency	Wet beriberi, occurring in chronic alcoholics, indistinguishable from alcoholic dilated cardiomyopathy.
Coxsackie B viral myocarditis	Chest pain, troponin elevation, arrhythmias. Survivors may progress to dilation.
Cocaine	Catecholamine effect.
Chagas disease	Long-term complication of a patient infected with *T. cruz*i (from endemic areas such as South America) who decades later develops dilated cardiomyopathy.
Doxorubicin toxicity	Dose-dependent and irreversible.
Trastuzumab	Dose-independent and reversible.
Peripartum cardiomyopathy	Responds to treatment.

Table 8.2: Causes of Dilated Cardiomyopathy

Transplant is required in most cases, though peripartum cardiomyopathy may respond to HFrEF treatment and trastuzumab toxicity is reversible simply with discontinuation of the drug.

Hypertrophic Obstructive Cardiomyopathy

Hypertrophic obstructive cardiomyopathy is caused by **massive myocyte hypertrophy**, **haphazard disarray** of myocytes (they criss-cross each other instead of running longitudinally), **myofiber disarray** (contractile elements are also disarrayed within individual myocytes), and **fibrosis**. Formerly known as subaortic stenosis, HOCM is the new, more accurate term for the condition. The key to understanding this diagnosis (as well as to understanding its former name) is the anatomic change that occurs near the left ventricular outflow tract. There is a disproportional thickening of the ventricular septum—a **septal hypertrophy**. Because the aortic valve and mitral valve both arise from the fibrocollagenous septum, they originate very near to one another, at the ventricular outflow. The septal hypertrophy causes two problems—subacute aortic stenosis and sudden occlusion of the outflow tract. First, there is indeed subaortic stenosis—a narrowing of the lumen of the ventricular outflow tract that is below the aortic valve. That narrowing of the lumen increases resistance, just like aortic stenosis does, just a little below the aortic valve. This is why HOCM will demonstrate **concentric hypertrophy** (sarcomeres added concentrically, fatter myocytes) throughout the ventricle **in addition to septal hypertrophy**. Second, the mitral valve flops down into the ventricle during diastole. It originates at the fibrocollagenous septum with the aortic valve, above the ventricular outflow tract, and flops down over the septal hypertrophy and the ventricular outflow tract. This isn't an issue when there isn't subaortic stenosis/septal hypertrophy, but it can be a really big issue if there is septal hypertrophy/subaortic stenosis. When the ventricle contracts, the blood is ejected up and out through the aorta. The mitral valve is supposed to be free to move, and the force of blood pushes it up out of the way. But if the mitral valve gets stuck on the outflow tract, the force of ejection may serve only to keep it stuck on the ventricular outflow. With the outflow obstructed and the atrium not obstructed, all the blood goes into the atrium. No distending force in the aorta, no recoil force from the aorta, no forward-driving perfusion pressure, which results in **sudden cardiac death**.

HOCM is caused by mutations in any one of several genes that encode **sarcomeric proteins**, and is inherited in an **autosomal dominant** fashion. There are more than 400 known mutations in nine genes, all resulting in the same septal hypertrophy. Some of the gene mutations that lead to HOCM, accounting for over 75% of cases, are (in descending order of prevalence) the gene encoding β-myosin heavy chain (β-MHC), followed by the genes encoding for cardiac TnT, α-tropomyosin, and myosin-binding protein C (MYBP-C).

Because there is concentric hypertrophy secondary to the subaortic stenosis / septal hypertrophy, the heart will become thicker and stiffer—less compliant. Stiff ventricles present with an **S4** heart sound (the sound just before the closure of the mitral valve, just before S1, as atrial kick delivers an injection of blood into and against a rigid ventricle). The subaortic stenosis is decreased area with normal flow, so there will be a sound similar to aortic stenosis—a **crescendo decrescendo murmur** heard over the aortic position (second intercostal space right sternal border). The way you can tell HOCM apart from aortic stenosis is by performing maneuvers that increase the blood in the heart. By **increasing the blood in the heart**, the ventricle widens by definition, moving the asymmetric septal hypertrophy away from the unaffected ventricular wall, alleviating the subaortic stenosis—the **murmur gets better**. Oh, and HOCM presents **in children and young adults**, while aortic stenosis is a disease of the elderly.

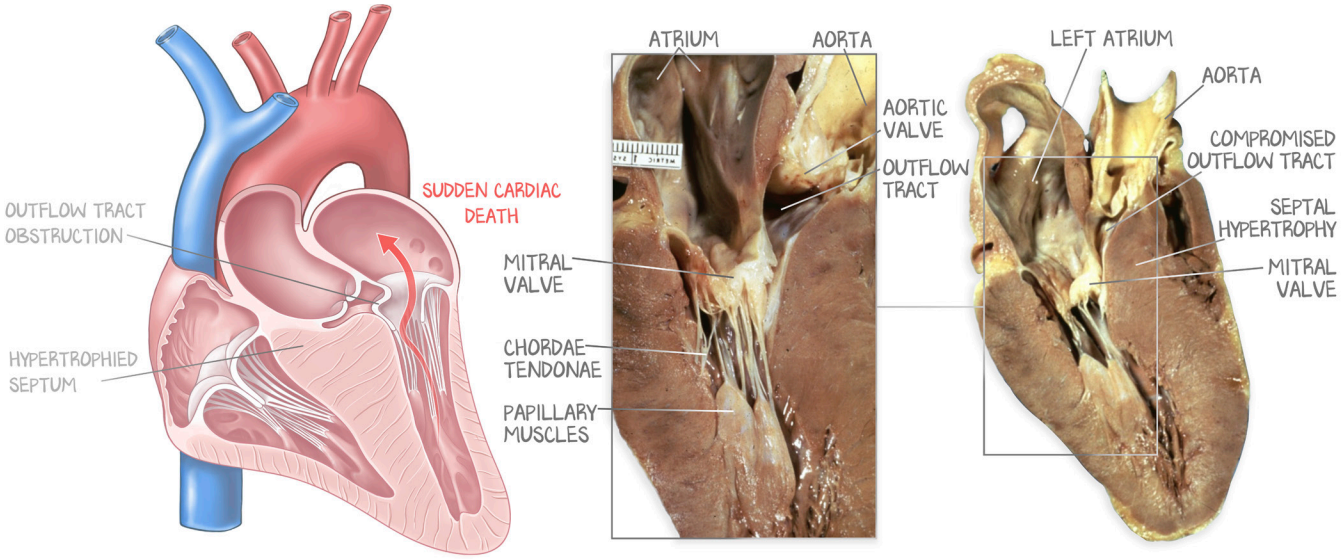

Figure 8.2: Hypertrophic Obstructive Cardiomyopathy

HOCM is confirmed with an echocardiogram. If a patient is diagnosed with HOCM they are referred for cardiology consultation for consideration of things above the level of Basic Sciences. HOCM is treated by alleviating the subaortic stenosis as much as possible. That means adding preload. The human can't be guzzling sugar-free beverages constantly to maintain preload, so it is achieved by **avoiding dehydration** and **heart rate reduction**. The longer the heart spends in diastole, the more filling time there is, the more volume there will be in the ventricle. To keep the heart rate down, there must be the **avoidance of high-intensity athletics**—avoidance of tachycardia. To achieve this medically, a **rate-control agent** may be added. β-blockers (metoprolol) or nondihydropyridine calcium-channel blockers (diltiazem or verapamil) are usually used. Of course, since the problem is the asymmetric septal hypertrophy at the outflow tract, surgical removal of the hypertrophy is an option.

A biopsy will show **myocyte hypertrophy**, **disarray of myocytes**, and interstitial **fibrosis**.

Restrictive Cardiomyopathy

In restrictive cardiomyopathy, something gets into the myocardium—between the cardiac myocytes—that isn't supposed to be in the myocardium. In effect, that something prevents the ventricle from accepting blood during diastole. This is similar to a stiff ventricle caused by concentric hypertrophy of myocytes that make a big and beefy heart, but not the same because there is not a stiff ventricle because of a thicker myocardium—there is no hypertrophy of myocytes or of myocardium. In fact, in regard to this lesson, where cardiomyopathy is an anatomic outcome of an underlying disease, restrictive cardiomyopathy represents the *other one*. The anatomic features of restrictive cardiomyopathy are that there is neither dilation (the volume doesn't change) nor hypertrophy (the myocardium's thickness doesn't change). Functionally, ventricular contraction is retained at a normal function, but **fails to relax**. Because there is a failure to relax in diastole, there is impaired filling in diastole. Because there is a retained ventricular contraction, lots of blood is ejected during systole. That means less blood in during diastole, more blood out during systole, resulting in an **elevated ejection fraction** (> 70% in most; > 90% is possible).

The diagnosis is actually quite difficult to make. Echocardiogram can show the elevated ejection fraction and may even show a **speckled appearance**. Cardiac **MRI** is usually required to identify a spot to biopsy. **Endocardial biopsy** is required for confirmation, though the etiology is usually known in advance, having presented not only with the restrictive cardiomyopathy but with other symptoms of the underlying etiology. The biopsy will show **normal myocytes** with extra stuff in between them.

A high ejection fraction does NOT mean diastolic dysfunction. Patients who have diastolic dysfunction do not need to have an elevated ejection fraction. Patients who have an elevated ejection fraction are exhibiting restrictive physiology, and should be suspected of having a restrictive cardiomyopathy (or one of its mimickers like constrictive pericarditis). The causes of restrictive cardiomyopathy can be remembered either by the mnemonic that follows, or by the sing-song in the video—sarcoid, amyloid, hemochromatosis, cancer and fibrosis (Oxford comma omitted here in order to match the sing-song in the video). Sarcoidosis is the infiltration of the myocardium by granulomas (discussed in detail in the Pulmonary module and hinted at in the MSK module). Amyloidosis is the deposition of excess protein, seen in conditions that produce excess protein, such as multiple myeloma (discussed in detail in the Heme/Onc module). Hemochromatosis is a disease of iron excess (discussed in the Gastrointestinal module). Cancer and fibrosis is a collective generic term that Dr. Williams uses as a catch-all for "other," which includes things like Loeffler endocarditis, endomyocardial fibroelastosis, radiation fibrosis (from treating cancer) and nearby mediastinal cancers that invade locally.

Some causes of restrictive cardiomyopathy are low-yield but commonly tested. There is an overlap between Dr. Williams's method and this one. This one is popular, but less effective.

	DIAGNOSIS	LOOK FOR
P	Post-radiation fibrosis	Previous cancer treatment (look for lymphoma).
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L	Loeffler endocarditis	Endomyocardial fibroelastosis + peripheral eosinophilia.
E	Endomyocardial fibroelastosis	Tropical disease showing a progressive subendocardial fibrosis from the apex to the atrioventricular valves.
A	Amyloidosis	Deposition of protein, either primary amyloidosis or senile amyloidosis.
S	Sarcoidosis	Granulomas stiffen ventricles.
H	Hemochromatosis	Iron overload, bronzing skin, early cirrhosis, can also cause dilation.

Table 8.3: Restrictive Cardiomyopathy Causes
Puppy leash, or P-LEASH. *Endocardial fibroelastosis involves only the endocardium, and is rapidly fatal.

Other Myocardial Stuff #1: Takotsubo

Takotsubo cardiomyopathy is a disease that is not well understood, and is named for its classic appearance on ventriculogram. For unclear reasons, the left ventricular apex is most often affected, leading to "apical ballooning" that resembles a "takotsubo," Japanese for "fishing pot for trapping octopuses." The octopus trap has a structure that is similar to the classic systolic ventriculogram.

This condition tends to occur in **old women** and in response to **emotional stress**. Thought to be related to a disproportionate catecholamine discharge, the acute presentation is nearly identical to a myocardial infarction. That is because the apex, the left ventricle, acts as if there were an ischemic event. The patient complains of chest pain and will **demonstrate ST segment elevations** (the gold standard on EKG to diagnose a myocardial infarct), but will have **clean coronaries** (and on licensing exam, no risk factors for coronary artery disease). When myocardium does suffer an ischemic insult, the myocardium becomes stunned. **Stunned** myocardium **doesn't move**. Dead myocardium doesn't move. So on echocardiogram and ventriculogram (which is done at the same time as the angiogram for the coronary arteries) there will be **apical ballooning—**the apex does not contract, so does not eject blood up and out the outflow tract. The rest of the ventricle does contract, sending blood forward through the aorta and back into the stunned apex. Because the apex doesn't contract while the rest of the ventricles do, the apex appears rounded, like the fishing pot for trapping octopuses in Japan.

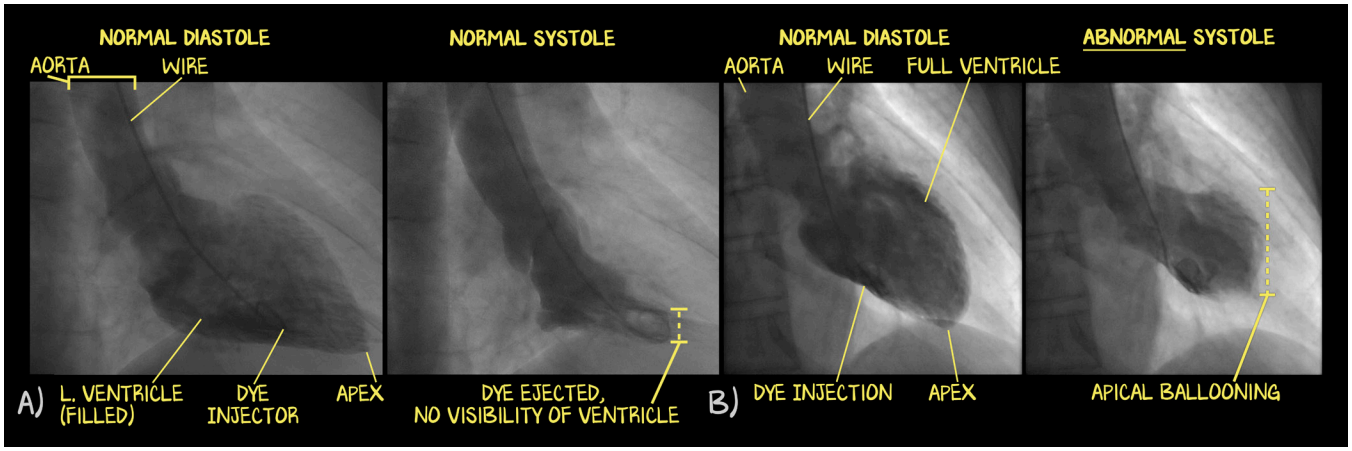

Figure 8.3: Takotsubo
(a) A ventriculogram taken at the end of diastole and systole demonstrates a heart of normal size, shape, and volume on diastole, then ejection of all the dye at the end of systole. The dye is injected through a wire into the ventricle, so the dye's shape represents the shape of the lumen—the ventricular wall itself cannot be seen. (b) A ventriculogram of a patient with takotsubo cardiomyopathy demonstrates normal volume and shape in diastole but the failure to eject blood in systole, and the apex changes from pointed to rounded. (See the supplementary video where Dr. Williams shows you what these look like.) Side note: the ventricle of the takotsubo patient appears larger than normal because the magnification is different in each sample. The ventriculograms in (a) and (b) are from different patients; compare the size of the vertebrae (left side of image).

Unlike dilated cardiomyopathy, takotsubo resolves spontaneously. While the myocardium is stunned, ventricular arrhythmias may arise. Over time, the patient returns to normal.

Myocarditis

Myocarditis is an inflammation of the myocardium. Inflammation means inflammatory cells on biopsy. Myocardium means there will be myocytes. A myocarditis may lead to a cardiomyopathy. It is included in this lesson because cardiomyopathies are problems of the myocardium, as myocarditis is a problem of the myocardium. While the focus of this lesson is on the three cardiomyopathies, we needed to include this somewhere, and here was the opportunity.

Inflammation of the myocardium can present just like a myocardial infarction—chest pain, troponin elevations that can get really high, and even ST segment changes—just like takotsubo cardiomyopathy. This often prompts an angiogram, which will reveal clean coronaries. But where takotsubo cardiomyopathy presents with apical ballooning and often returns to normal, myocarditis can have varying severity of consequences and recovery. The etiology is often undetermined. Even endomyocardial biopsies may be unrevealing, as the myocardial involvement is almost always (regardless of etiology) sporadic. Suspect myocarditis when the patient clearly has a heart attack, yet has clean coronaries and no risk factors for vascular disease. This includes cardiogenic shock or the development of new arrhythmias.

There are three known etiologies of myocarditis: viral, giant cell, and Chagas disease.

Viral myocarditis is caused by **coxsackie B**. Most cases of myocarditis do not get a biopsy, and so do not have a known cause. If biopsied, viral myocarditis will show a **lymphocytic infiltrate**—there are lymphocytes **between** cardiac myocytes. Inflammatory cytokines produced in response to myocardial injury can also cause **myocardial dysfunction** that is **out of proportion** to the degree of actual myocyte damage. The patient's heart function is compromised, resulting in dilation or signs of failure. A potential sequela of viral myocarditis is dilated cardiomyopathy, though most cases resolve without sequelae.

Giant cell myocarditis is a rare and rapidly fatal form of myocarditis. It is often used on licensing exams to trip up learners regarding the histology of viral myocarditis. In giant cell myocarditis there are **multinucleated giant cells** (ramped-up, fused macrophages) surrounded by the **lymphocytes** that drive macrophage activation. Whereas viral myocarditis will have lymphocytes between cardiac myocytes, giant cell myocarditis shows the giant cells and lymphocytes **within fibrosis** (where formerly there were cardiac myocytes) at the **edge of cardiac myocytes**. Over time, the lymphocytes and giant cells progress into the cardiac myocytes, replacing the heart with scar.

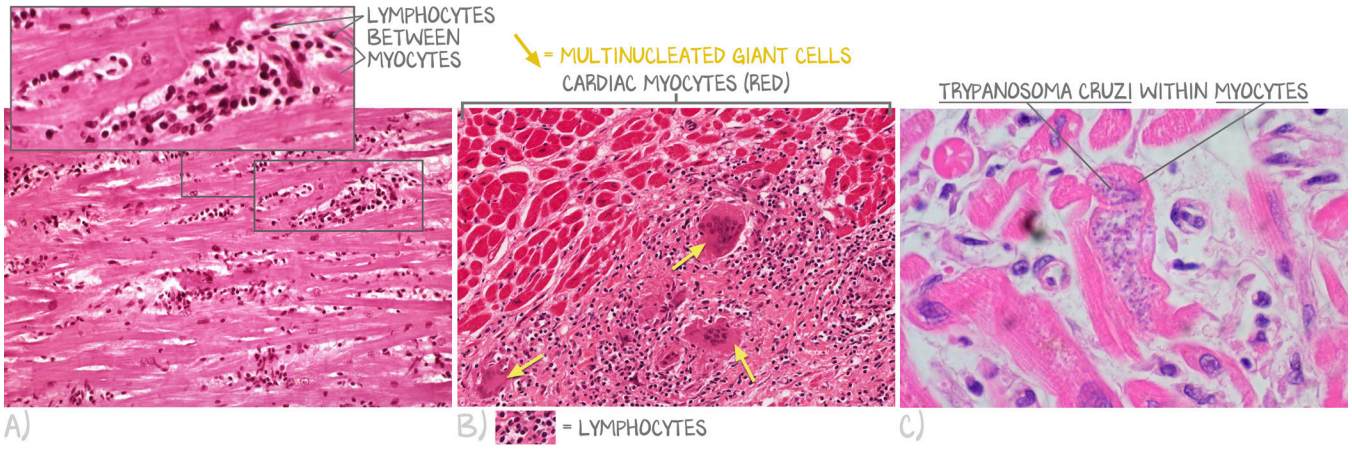

Figure 8.4: Myocarditis
(a) A viral myocarditis demonstrating lymphocytes between cardiac muscle fibers. There is minimal lymphocytic reaction (compared to (b)), but many small nuclei (dark purple dots) are scattered between the cardiac myocytes. (b) Giant cell myocarditis is rapidly fatal. The histologic hallmark is cardiac myocytes near multinucleated giant cells, which are often surrounded by lymphocytes and fibrosis. (c) The myocarditis of Chagas disease. A cardiac myocyte is distended with trypanosomes.

Nonviral agents are also important causes of infectious myocarditis, particularly the protozoan *Trypanosoma cruzi*, the agent of **Chagas disease**. Yes, that is right: Chagas disease refers both to the chronic fibrosing myocarditis that leads to dilated cardiomyopathy after decades of silent infection AND it can cause an acute myocarditis. Most often, the infection of the heart goes unnoticed. We taught you in Microbiology not to learn this form of Chagas disease, and are making that suggestion again.

DISEASE	HIGH YIELD
Dilated cardiomyopathy	Dilation of all four chambers, eccentric hypertrophy Reduced ejection fraction, arrhythmias Titin genes, anthracyclines, trastuzumab Alcohol, cocaine, Chagas disease (chronic)
Hypertrophic obstructive cardiomyopathy	Sarcomere genes, sarcomere disarray, myocyte disarray No dilation of chambers, asymmetric septal wall hypertrophy Outflow tract obstruction at low ventricular volumes Young athlete who has syncope, fam h/o sudden cardiac death
Restrictive cardiomyopathy	No dilation of chambers, no wall hypertrophy Impaired diastolic filling, high pressures, and low volumes Huge ejection fractions in addition to diastolic dysfunction Sarcoid, amyloid, hemochromatosis, cancer and fibrosis (Loeffler's)
Takotsubo	Elderly white women with obvious ST segment elevation myocardial infarction (a 100% of a coronary vessel) but clean coronaries on cath Ventriculogram presents with apical ballooning
Viral myocarditis	Coxsackie B, lymphocytic infiltrate High troponins, behaves like STEMI with similar risks
Chagas myocarditis	*Trypanosoma cruzi* infection, seen in cross-section of muscle South America High troponins, behaves like STEMI with similar risks

Table 8.4: High-Yield Review